TABLE 5-continued

Summary of Total Amount of Theophylline and Its Metabolites Excreted in Urine Over 72 Hours Following an Oral Dose of 400 mg Theophylline Coadministered With 80 mg Febuxostat or Matching Placebo

	Theophylline (mg)	1,3-Dimethyluric acid (mg)	1-Methyluric acid (mg)	1-Methylxanthine (mg)	3-Methylxanthine (mg)
SD	18.1	23.3	4.0	7.6	9.5
CV %	52	22	127	19	35
			Theophylline + Placebo (Regimen B)		
N	23	23	23	23	23
Mean	35.0	114.8	56.2	0.1	30.9
SD	16.8	32.2	17.4	0.4	11.6
CV %	48	28	31	337	38

Regimen A: Febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.
Regimen B: Matching placebo for febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

As illustrated in Table 5 above, the mean amount of parent drug (i.e., theophylline) excreted in the urine over a 72 hour interval were comparable between regimen arms and consistent with the literature. See Melethil S et al., *Res Commun Chem Pathol Pharmacol.,* 1982; 35(2):341-4. The mean amounts of 1,3-dimethyluric acid and 3-methylxanthine were also similar between the 2 regimens. In contrast, 1-methyluric acid decreased and 1-methylxanthine increased in subjects administered theophylline with febuxostat compared with those subjects administered theophylline with placebo.

A statistical analysis of the data was also performed. The effects of sequence, period, and regimen on theophylline T_{max}, ln(C_{max}), ln(AUC[0-tlqc]), and ln(AUC[0-inf]) following coadministration of febuxostat or placebo were assessed. None of the aforementioned effects were statistically significant on the pharmacokinetic parameters (P>0.05) observed in the experiment. Further, the bioavailability of theophylline coadministered with febuxostat (Regimen A) relative to that of theophylline with placebo (Regimen B) was assessed via point estimates and 90% confidence intervals for the ratios of the central values for C_{max}, AUC(0-tlqc), and AUC(0-inf), and is summarized in Table 6.

TABLE 6

Relative Bioavailability of Febuxostat Following Administration of a Single Oral Dose of 80 mg Febuxostat

Parameter	Point Estimate	90% Confidence Interval
	Regimen A vs Regimen B	
Cmax	1.03	(0.917, 1.149)
AUC(0-tlqc)	1.04	(0.927, 1.156)
AUC(0-inf)	1.05	(0.924, 1.189)

Regimen A: Febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.
Regimen B: Matching Placebo for febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.
Note:
The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm transformed data.

From the statistical analyses of the pharmacokinetic data, the point estimates for theophylline C_{max}, AUC(0-tlqc), and AUC (0-inf) were close to 100%, and the 90% confidence intervals for the ratios were within the bioequivalence limit of 0.80 to 1.25.

The results of this experiment showed that the maximum observed theophylline concentration (Cmax) and exposure to theophylline (AUC) were comparable between treatment with febuxostat and treatment with placebo. Therefore, no adjustment of the theophylline dose was needed when coadministered with febuxostat.

What is claimed is:

1. A method of treating hyperuricemia in a patient in need of treatment thereof, the method comprising the steps of:

administering to a patient suffering from hyperuricemia and at least one second disease state, a therapeutically effective amount of 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof, wherein the subject is also receiving concomitant administration of theophylline to treat the at least one second disease state, and

further wherein (i) the administration of 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof, to the patient does not result in theophylline toxicity to the patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

2. The method of claim **1**, wherein the second disease state is asthma.

3. The method of claim **1**, wherein the patient is further suffering from at least one third disease state, wherein the third disease is gout.

4. The method of claim **1**, wherein the theophylline dosage amount ranges from about 95% to about 105% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

5. The method of claim **1**, wherein the theophylline dosage amount ranges from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

6. The method of claim **1**, wherein the patient suffering from hyperuricemia and the at least one second disease state is previously administered theophylline prior to initiation of treatment with 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid.

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